A STUDY ON CLINICOPATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CARCINOMA

Dissertation Submitted
for the Degree of
MASTER OF SURGERY
Branch I
(GENERAL SURGERY)

THE TAMIL NADU
Dr.M.G.R. MEDICAL UNIVERSITY
CHENNAI

SEPTEMBER 2006

COIMBATORE MEDICAL COLELGE

COIMBATORE.

CERTICATE

Certified that this is the bonafide dissertation done by

Dr.B.KESAVAN

and submitted in partial fulfillment of the requirement for the

Degree of MASTER OF SURGERY

Branch I (GENERAL SURGERY)

of The Tamil Nadu Dr.M.G.R. Medical University, Chennai.

DATE :

PROFESSOR AND HEAD
DEPARTMENT OF SURGERY
COIMBATORE MEDICAL COLLEGE

DATE :

DEAN
COIMBATORE MEDICAL COLLEGE
COIMBATORE

DECLARATION

I solemnly declare that this Dissertation on **"A STUDY ON CLINICOPATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CARCINOMA"** was done by me at Coimbatore Medical College Hospital, Coimbatore under the guidance and supervision of **Prof.DR.K.P.ARUNKUMAR, M.S.**

Place :

Date : **DR.B.KESAVAN**

ACKNOWLEDGEMENT

I am extremely grateful to **Dr. T.P. KALANITHI, M.D.** Dean of Coimbatore Medical College hospital, Coimbatore., for permitting me to utilize the hospital facilities for my dissertation work.

I express my sincere and heartfelt thanks to the Head of the Department of Surgery, Professor **Dr. K.P.ARUNKUMAR.M.S.,** for giving me guidance and help in preparing this dissertation.

I am also very grateful to **Prof.Dr.R.INDRA PRANESH, M.D, Path.** and Asst professor **Dr.VIMALA, M.D. Path, Dr.DHANALAKSMI M.D.Path.** for the help and guidance in the course of the study.

I hereby submit my sincere thanks to **Dr.MUTHU KRISHNAN, M.D. (RT)** and **Dr. AKILA MD (RT),** for there helps in oncology Department.

I also express my thanks to unit assistant professors for giving me their support and help during my studies.

Finally, I place on record my sincere thanks to the patients whose co operation made this work possible.

CONTENTS

INTRODUCTION

Locally Advanced Breast Carcinoma represents 30-50% of newly diagnosed Breast Cancer in medically underserved population all over the world[1].

Historically breast cancer believed to be a local manifestation of a systemic disorder until Keen demonstrated that it began locally and spread but today it is claimed that it is already disseminated when the diagnosis is made and local treatment is useless. Most cancer at that time were huge that necessitated radical approach and leads to the development of Halsted radical mastectomy. In 1894 Keen started seeing early breast cancer and with 3 years follow up after surgery he claimed it as cure and in 1985 Fisher claimed 5yrs result for breast preserving operations. With all developments breast cancers are now classified as early and advanced breast carcinomas and it becomes important to individualize patients for treatment best suited to a given woman. According to AJCC (American Joint Committee on Cancer) Cancer Staging Manual, Early stage invasive breast cancer – Stages I (tumor <2 cm in

size, axillary node-negative) and II (positive but ipsilateral and mobile axillary nodes, or tumor size >2 cm); a tumor >5 cm must be node-negative to be considered early stage Locally advanced (extensive axillary nodal disease, supraclavicular nodal involvement, direct tumor extension to the chest wall or skin) or inflammatory breast cancer - Stage III disease Metastatic breast cancer - Stage IV disease.

Locally advanced breast carcinoma is a clinical scenario considered as inoperable either because they were technically unresectable or an extremely high risk of metastasis, local recurrence and or death despite aggressive surgical resection. Although multimodality therapy employing combination of systemic and loco regional therapy became the treatment of choice, the optimal sequencing of the individual component was not well defined[2]. Based on the concept of breast cancer as a systemic disease, chemotherapy was introduced into the treatment of LABC in 1970 and more recently major clinical response to induction chemotherapy were noted in the majority of patients at the time of surgery and long term outcome was associated with significant higher disease free survival and over

all survival[3]. Hence neoadjuvant chemotherapy followed by surgery and radiotherapy is now emerging globally as the most common approach for LABC including IBC[4].

AIM OF STUDY

Neo adjuvant chemotherapy in locally advanced breast cancer produces clinical and pathological changes that frequently reduces the size of the tumor correlating with response of the distant metastasis and therefore predicting outcome of the breast cancer patients.

1. To study the clinico pathological response of primary tumor to the neoadjuvant chemotherapy.
2. To evaluate the improvement in operability
3. To assess disease free survival.

SURGICAL ANATOMY OF BREAST

The breast or mammary gland is a modified sweat gland situated in the superficial fascia on the anterior chest wall. It is rudimentary in male. In the female, it starts enlarging at and after the age of puberty under hormone Influence.

EXTENT[5] :

Vertical : 2nd to 6th Rib

Horizontal : the lateral Margin of the Sternum to Mid Axillary line.

Axillary tail of Spence : This is the Prolongation from the upper outer portion of the deep surface of the mammary gland. It is in the direct contact with the main lymph node of the breast. (anterior axillary nodes.)

ARCHITECTURE OF THE BREAST

The skin covering the breast presents as erectile conical projection called the nipple at the level of the fourth intercostals space. The nipple is pierced by 15 to 20 major lactiferous ducts. The skin surrounding the base of the nipple forms a circular area called the areola, rich in modified sebaceous glands appear as nodular elevation during pregnancy and lactation and

are called ‘Montgomery’s tubercles.’ The skin of the nipple and areola is devoid of hair and there is fat subjacent to it.

The glandular tissue is composed of acini (alveoli) which make up lobules aggregation of which form the lobes of the gland. The gland consists of 15 to 20 lobes. The lobes are arranged in a radiating fashion and each lobe is drained by a separate lactiferous duct. The dilatation of each duct near its termination is called the lactiferous sinus.

Acinar epithelium is cuboidal in resting phase and columnar during lactation.

The supporting frame work of the gland is the stroma and is partly fibrous and partly fatty. The fibrous stroma forms septa known as the suspensory ligament of Asley cooper which anchor the gland to the overlying skin and to the underlying pectoral fascia.

BLOOD SUPPLY OF THE BREAST[6]:

Breast has extensive blood supply. This is derived from,

1. The lateral thoracic, superior thoracic and acromio – thoracic, branches of subclavian artery.

2. The perforating cutaneous branches of the internal mammary artery to the second, third, and fourth intercostals spaces.

3. The lateral branches of the second, third, fourth intercostals arteries.

VENOUS DRAINAGE OF THE BREAST :

The veins follow the arteries. There is a venous circle beneath the areoloar skin called circulous venosum. There is also a deeper venous circle at the base of the gland and both circles communicate each other. They drain into the internal mammary, axillary and posterior intercostals veins.

NERVE SUPPLY OF THE BREAST :

The breast is supplied by the anterior and lateral cutaneous branches of the second to the sixth nerves. The nerves convey sensory fibres to the skin and autonomic fibres to smooth muscles and blood vessels.

LYMPHATIC DRAINAGE OF THE BREAST[7] :

The breast is drained by two sets of lymphatics.

1. Lymphatics of the skin of the breast.
2. Lymphatics of the parenchyma of the breast.

LYMPHATICS OF THE SKIN OF THE BREAST :

The lympahtics drains the Integuments over the breast, but not the nipple and areola. These lymphatics passes radially and end in the surrounding lymph nodes, axillary, supraclavicular, and internal mammary nodes.

The lymphatics of the skin communicate across the midline and a unilateral disease may become bilateral by this route.

LYMPHATICS OF THE PARENCHYMA OF THE BREAST :

These lympatics drains the parenchyma of the breast and the nipple and areola.

The subareolar lymph plexus of sapey is a collection of large lymph vessels communicate with the lymphatics of the breast tissue. It is not a collecting zone for the breast lymph.

The axillary nodes receive about 75% of lymph, draining the breast tissue. Among the axillary nodes most of the lymphatics are in the anterior group (closely related to axillary tail) and partly in the posterior and apical group. From there, they drains to the central and lateral group and through them to the apical group (High axillary lymph nodes.)

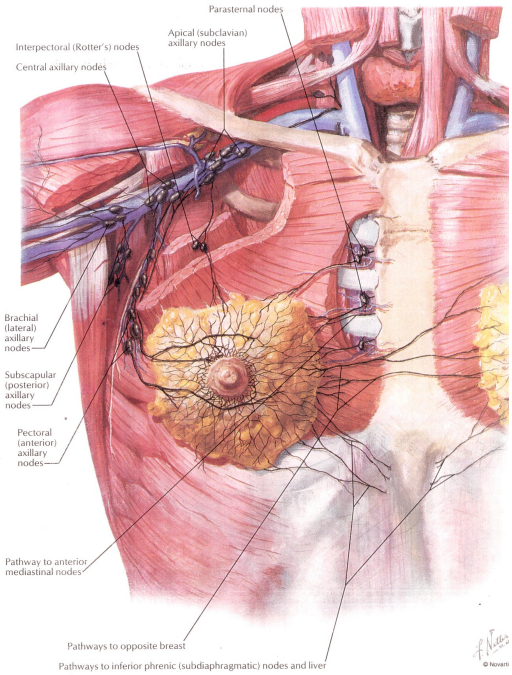
To standardize the extent of axillary dissection, the axillary space of lymph nodes is arbitrarily divided into three levels.

LEVEL I NODES :

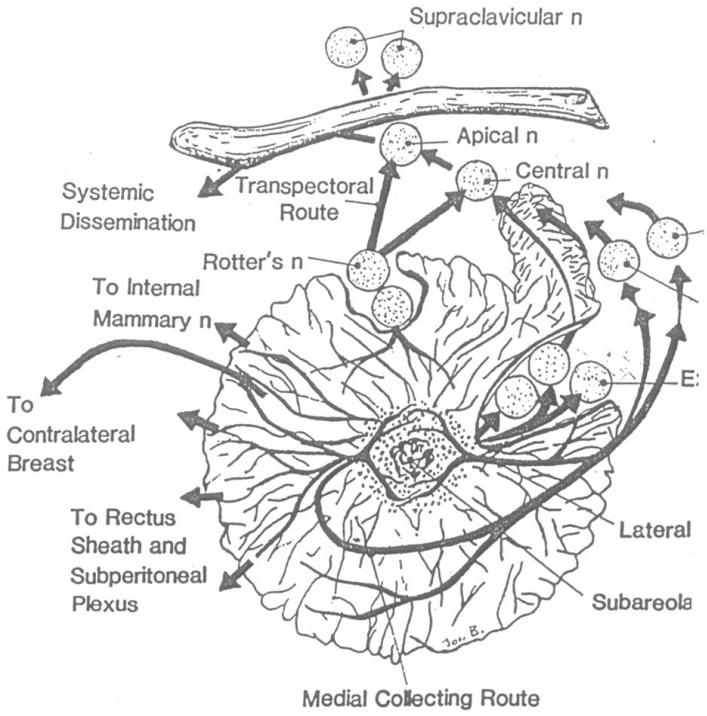
Lateral to lateral border of Pectoralis Minor muscle including external mammary, scapular and central axillary group of nodes.

LEVEL II NODES :

It lies under the pectoralis minor muscle, including some of the nodes of central axillary group.



ANATOMY OF AXILLARY LYMPH NODES AND LYMPH VESSELS



SCHEMATIC REPRESENTATION OF ROUTES OF LYMPHATIC DRAINAGE

LEVEL III NODES :

It lies medial to the medial border of pectrolis minor muscle including apical lymph nodes.

SITUATION OF THE AXILLARY NODES

ANTERIOR SET :

Situated along the lateral thoracic vein under the anterior axillary fold lying mainly on the third rib in close contract with the axillary tail of spence.

POSTERIOR SET :

These lymph nodes lie along the posterior axillary fold in relation to the subscapular vessels.

LATERAL SET :

These lymphnodes lie along the upper part of the humerus in relation to the axillary vein.

CENTRAL SET :

Situated in the fat of the upper part of axilla. The intercosto brachial nerve plexus outwards among these nodes.

APICAL SET :

Also called the ‘infraclavicular set’ bounded below by the first Intercostal space, behind by the axillary vein, in front by the costo coracoid membrane.

1. A single lymph trunk leaves the apical group on each side of the subclavian trunk and enters at the junction of the internal jugular and subclavian vein (or) it may join the thoracic duct on the left side of neck.

2. About 20% of the lymph from the breast drained into the internal mammary nodes.

3. About 4% of the lymph from the breast drains into posterior intercostals Nodes along the perforating branches of the internal mammary artery and along the lateral perforating branches of the intercostals vessels.

4. Lymphatics from the lower and inner quadrant of the breast may communicate with the sub diaphragmatic and sub peritoneal lymph vessels after crossing the costal margin and then piercing the abdominal wall through the upper part of the linea alba.

PATHOLOGY OF BREAST CARCINOMA

Because of more complex structure, the greater volume and it's extreme sensitivity for endocrine influences the female breast is more prone for various pathological diseases than the rudimentary male breast.

Breast malignancy are basically classified into two types

Non invasive → -DCIS
Non invasive → -LCIS

Invasive

NON-INVASIVE (IN SITU) CARCINOMA :

(A) INTRADUCTAL CA (DCIS) [8]:

With the advent of mammography, it now constitutes 22-80% of carcinoma's. it is defined as malignant population of cells that lack the capacity too invade the basement membrane and incapable of distant metastasis. The Cells are large and pleomorphic vacuolated macro phages contains hemosiderin pigments represents the comedo plugs. Calcification may be seen.

There are five subtypes[9], They are :

a. Comedo carcinoma

b. Solid

c. Cribriform

d. Papillary

e. Micropapillary

Among these, comedo carcinoma is more malignant.

COMEDO CARCINOMA :

Usual findings are :

1. Variable cell yield
2. Neoplatic cells in irregular aggregates and singly.
3. Large, pleomorphic cells showing obvious malignant features.
4. Necrotic debris, lymphocytes and vacuolated macrophages.

PAPILLARY TYPE[10]:

The smear has abundant papillary aggregates with central fibrovascular core. Columnar cells in rows, palisades and single. Bare nuclei of benign type is absent. Variable nuclear enlargement pleomorphism and atypia seen. Necrotic debris present.

CRIBRIFORM TYPE:

Epithelial cells relatively cohesive forming large mono layered sheets are seen. Mild epithelial atypia and debris is seen. Macrophages often with hemosiderin pigment is present.

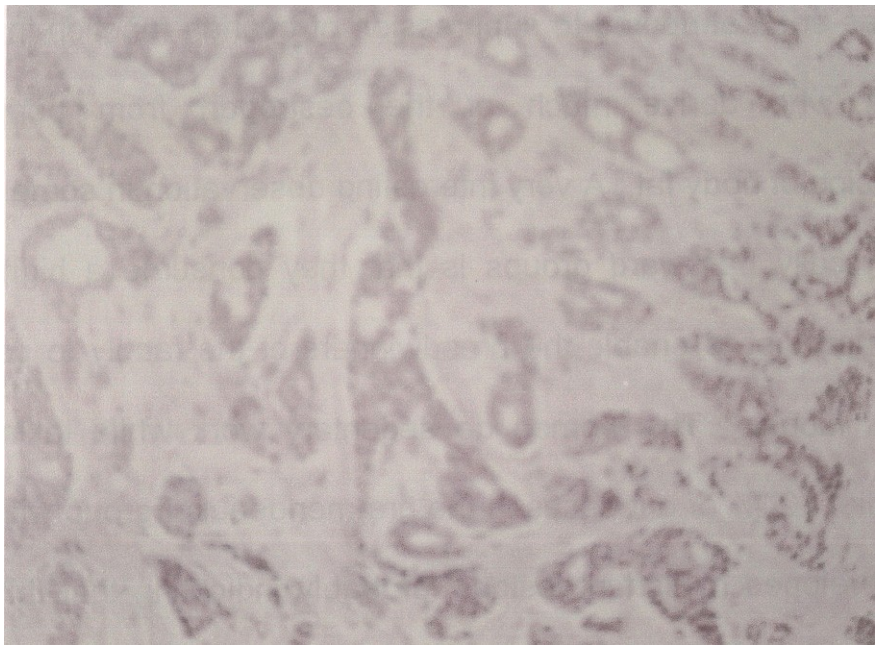
(B) LOBULAR CA IN SITU (LCIS) :

There is proliferation of loosely cohesive cells in one or more terminal ducts / acini. It is frequently multifocal and bilateral, the lesion is a marker for invasive carcinoma.It is difficult to define cytological criteria for this diagnosis in FNA smear. Intracytoplasmic neolumina is the most useful clue to the cytological diagnosis (Salhany and Page)[11].

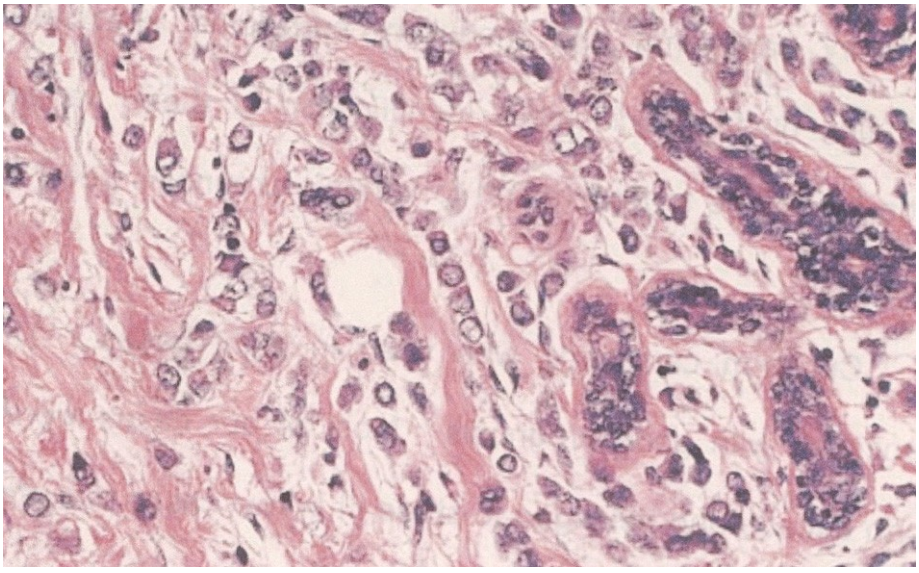
II INVASIVE CARCINOMA :

Features in breast needle aspirates of malignant lesions are

1. Loss of cell adhesion
2. Cellularity high
3. Lack of stripped nuclei
4. Increased cell size
5. Pleomorphism
6. Variable nuclear chromatin often with prominent nucleoli occasionally a lymphocyte response.



FNAC PICTURE OF INVASIVE DUCTAL CARCINOMA



FNAC PICTURE OF INVASIVE LOBULAR CARCINOMA

(A) INVASIVE DUCTAL CARCINOMA :

Common type. Incidence 65-80% of all mammary cancers. There may be nipple retraction, dimpling of skin, fixity to muscle chest wall. Histologically, cells lining the duct are disposed in cords, solid cell nests tubular glands, anastamosing masses.

Criteria for diagnosis:

1. High cell yield
2. A dingle population of atypical epithelial cells
3. Irregular angulated clusters of atypical cells
4. Reduced cohesiveness of epithelial cells
5. Nuclear enlargement and irregularity
6. Single cells with intact cytoplasm
7. Absence of single nare nuclei
8. Necrosis, important if present

A scirrhous cancer may yield very few cells or no cells at all. Nuclei irregular shape and irregular contours is diagnostic of malignancy. However the cell population can be quite monomorphous and nuclear abnormalities may be suitable[12].

In poorly differentiated carcinoma dissociation of cells may be total and smear may resemble large cell lymphoma. Cells

usually have well defined cyto plasm, but infiltrating lobular carcinoma is an exception.

(B) INVASIVE LOBULAR CARCINOMA :

Peculiar feature is bilateral and multicentiric. Histologically, it consists of stands of infiltrating tumour cells, lossely disposed throughout the fibrous matrix. It have an abundant desmoplastic storma. The cells are seen in small groups and single file. The cells have often lost their cytoplasm and often show nuclear moulding.

The other findings are :

Poor cell yield.

Cytoplasm scanty, and indistinct.

Small dark nuclei with Irregularity in shape.

(C) MEDULLARY CARCINOMA :

Incidence 1-5%. It has soft empty feel to the needle. It often bleeds easily. Do not have striking desmoplasia The cytology is quite similar to comedocarcinoma. The smear is highly cellular. Irregular cell aggregates and single cells with lymphocytic infiltration is seen. Nuclei are large and pleomorphic. Histologically, solid syncytium like sheets of large cells with lymphocytic infiltration is present.

(D) COLLOID OR MUCINOUS CARCINOMA :

Occurs in old woman, slow growing, Macroscopically are well circumscribed with soft pale surfaces. Histologically , large lakes of amorphous mucin with scattered neoplastic cells are present.a small amount of fibrous stroma is also present. The cells are rather uniform and exhibit mild atypia. These tumor has better prognosis when compared to that of invasive ductal carcinoma.

(E) TUBULAR CARCINOMA[13] :

Macroscopically they are poorly circumscribed with hard in consistency and are small in size. Microscpically, it shows moderately cellular smears. Cells are predominantly in cohesive clusters. Epithelial with an angular shape and tubular pattern is present single bare nuclei are often present. An associated intra ductal carcinoma of cribriform type is seen in two third of cases. They have the excellent prognosis.

(F) PAGET'S DISEASE OF NIPPLE

There is invariably underlying ductal carcinoma in situ. Histologic hallmark is involvement of epidermis by malignant cells Background shows ketatin, squamous cells and inflammatory

cells. Abundant pale cytoplasm with distinct borders is seen. Nuclei show features of malignancy.

(G) INFLAMMATORY CARCINOMA :

There is thickening and erythema of the skin due to extensive intralymphatic spread of tumour causing lymph stasis and edema. The cytological pattern is similar to that of the common carcinoma Inflammatory cells are not seen. It is a rapidly progressive tumor and high propensity for early metastatic spread.

(H) SARCOMA[14] :

Smear from a tumour fragments of highly cellular stromal tissue of spindle cells which may show nuclear atypia and pleomorphism. There is variable number of sheets of epithelial cells. However definitive diagnosis is by biopsy. In angiosarcoma aspiration yields plenty of blood and tumour cells may be few in numbers. Most cells are in syncitial clusters but some are single[15].

RISK FACTORS FOR DEVELOPMENT OF BREAST CARCINOMA

1. Genetic and familial factors.
2. Hormonal factors.
3. Benign Breast disease.
4. Dietary and environmental influences.

1. GENETIC FACTORS[16] :

Only about 10% of breast cancers of human breast cancer can be linked directly to germ line mutations. The first to be identified was germ line mutations in tumour suppressor gene P 53.

Another Putative tumour suppressor gene – BRCA gene – 1 has been identified at the chromosomal locus 17q21 ; this gene encodes a zinc finger protein and the product therefore may function ad transcription factor. Women who inherit the mutant alleles of this gene from either parent have an approximately 85 to 90% life time chance of developing breast cancer. Men who carry this mutant alleles have increased incidence of prostate cancer but not usually the breast cancer.

A third gene BRCA – 2, which has been localized to chromosome 11, is associated with increased incidence of breast cancer in Men and women.

Even more important than the role these genes play in inherited forms of breast cancer susceptibility, may be their role in sporadic breast cancer. For example P53 gene in present in approximately 40 % of human breast cancer in acquired defect. IN small series of sporadic breast cancer, decreased expression of BRCA - 1 mRNA occurs. An abnormal cellular location of BRCA – 1 protein has also been found in some breast cancers.

2. FAMILIAL FACTORS :

A woman with a family history of breast cancer has an increased risk of developing breast cancer in her life time. The risk varies with the degree of relation of the patient, whether cancer developed in premenopausal (or) post menopausal period, unilateral (or) bilateral breast cancer and others.

The life time risk for a woman with affected mother (or) sister in as follows :

. Unilateral and post menopausal - 15-20%

. Unilateral & premenopausal - 25%

. Bilateral & Postmenopausal - 35-40%

. Bilateral & Premenopausal - 50-65%

Risk increased when more than one relative members involved by breast carcinoma.

3. HORMONAL FACTORS :

Breast Cancer is related to hormones and reproductive factors. The principle hormone is estrogen. Prolonged exposure of breast tissue to unopposed estrogen action increases the incidence of breast cancer.

. Age at Menarche

. Age at Menopause

. Parity and age at First child birth.

. External use of hormones.

. Oophorectomy.

HORMONAL FACTOR IMPLICATIONS :

Menarche : 20% decrease in risk for each year delay.

Menopause : Before 45 years, the risk is half compared to menopause after 55 years.

Parity : Nulliparous risk is twice more than parous women.

Pregnancy : After 30 years, the risk is 2 to 5 times more compared to pregnancy and child birth at 18 / 17 years.

Abortions : No protection.

Oophorectomy : Before 50 years decreases the risk of development of breast cancer.

ORAL CONTRACEPTIVES :

The most valuable analysis of increased risk of breast cancer, with oral contraceptive suggest that there is little, if any increased risk usually after prolonged use of Oral contraceptives for more than seven years.

4. DIETARY FACTORS :

The role of diet in breast Carcinoma is controversial. While there is associative links between total caloric intake and breast cancer risk, the strongest link is with high dietary fat intake. However within the range of delivery fat intake common in western countries, there is no convincing evidence that variations in dietary fat alter breast cancer risk. There is increased risk associated with moderate alcohol intake, increased risk associated with cigar smoking.

5. OBESITY :

Increased risk attributed to the synthesis of Oestrogens in fat deposits, especially in postmenopausal women.

6. RADIATION :

May be a risk factor in younger women,. Women who have exposed before the age of 30, the high dose radiation in the form of multiple fluroscopies (200-300 Gray) or treatment for Hodgkin's

lymphoma (<3600 Gray) may be substantially increased risk of breast cancer, whereas exposure after the age of 30, appears to have minimal iatrogenic effect on the breast.

7. BENIGN BREAST DISEASE :

Fibro cystic diseases with atypical hyperplasia are associated with increased risk of about 4.4 times the risk of developing breast cancer.

* Carcinoma of contralateral breast and endometrium are associated with increased risk of developing Breast cancer.

RISK FACTORS FOR BREAST CANCER

Major	**Minor**
1. Gender female >male	1. Early menarche
2. Age	2. Late menopause
3. Family history	3. Obesity
4. Personal history of contra lateral breast cancer.	4. History of radiation
5. Benign breast disease with epithelial atypia.	5. Late child birth

LOCALLY ADVANCED BREAST CARCINOMA-AN OVERVIEW

Locally advanced Breast Carcinoma is a term that refers to most advanced stage non metastatic breast tumors and encompass wide variety of clinical scenarios. Despite its decreasing frequency over the past several decades locally advanced breast carcinomas remains an important and challenging problem in clinical practice. M.D Anderson Cancer Center defines Locally advanced Breast Carcinoma as any advanced primary tumors that is greater than 5cms or that involves the skin or chest wall, advanced nodal stages that is patients with fixed axillary lymphnodes or ipsilateral supraclavicular, infraclavicular, or internal mammary nodal involvement and inflammatory carcinomas.. In TNM staging classification, LABC is represented by stage III A (To N_2, T_1/T_2-N_2, T_3N1/2) IIIB (74No-2) and IIIC disease (Any T, N_3)[17]. IBC constitutes T4d primary tumor designation and therefore stage III B disease.

TNM Staging System for Breast Cancer presented in the fifth edition of the AJCC Cancer Staging Manual,

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget)	Paget's disease of the nipple with no tumor Note: Paget's disease associated with a tumor is classified according to the size of the tumor.
T1	Tumor ≤2 cm in greatest dimension
T1mic	Microinvasion ≤0.1 cm in greatest dimension
T1a	Tumor > 0.1 cm but not > 0.5 cm in greatest dimension
T1b	Tumor > 0.5 cm but not > 1 cm in greatest dimension
T1c	Tumor > 1 cm but not > 2 cm in greatest dimension
T2	Tumor > 2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
T4a	Extension to chest wall, not including pectoralis muscle
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastasis
N1	Metastasis in movable ipsilateral axillary lymph node(s)
N2	Metastases in ipsilateral axillary lymph nodes fixed or

	matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N3	Metastasis in ipsilateral infraclavicular lymph node(s), or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s) and axillary lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)
Regional lymph nodes (pN)†	
pNX	Regional lymph nodes cannot be assessed (eg, previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells‡
pN0(i-)	No regional lymph node metastasis histologically, negative IHC
pN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster > 0.2 mm

pN0(mol-)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
pN1mi	Micrometastasis (> 0.2 mm, none > 2.0 mm)
pN1	Metastasis in one to three axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent$
pN1a	Metastasis in one to three axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent$
pN1c	Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent$,||
pN2	Metastasis in four to nine axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN2a	Metastasis in four to nine axillary lymph nodes (at least one tumor deposit > 2.0 mm)
pN2b	Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis

TNM Stage Grouping for Breast Cancer

Stage Grouping			
0	Tis	N0	M0
I	T1*	N0	M0

IIA	T0	N1	M0
	T1*	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

NOTE. Adapted with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, www.springer-ny.com.

Inflammatory Breast Carcinoma

It's a distinct clinical subtype of LABC. Primary IBC is relatively rare accounting for 0.5-2% of invasive Breast Cancer common in pre and perimenopausal women and rare in men. Pregnancy and lactation do no predispose to the development of IBC[18]. It is a rapidly progressive tumor and high propensity for early metastatic spread. Median survival of woman with IBC was significantly worse than for women with non inflammatory LABC (2.9 versus 6.4 years)[19.] Secondary inflammatory breast

cancers develop from neglected locally advanced Breast Cancers but should be distinguished as these may follow a more indolent course and can be treated as other LABC[20]

DIAGNOSIS AND STAGING

Clinical presentations of most of the Locally advanced Breast Carcinoma are

- Large tumors (>5cm)
- Extreme regional lymph node involvement
- Direct involvement of skin or underlying chest wall
- Tumors that are inoperable but without distant metastasis (including involvement of supra elevation lymph nodes)
- Inflammatory Breast Cancer)

Diagnosis of IBC is a clinical one and typically present with pain and a rapidly progressing, warm, tender, firm enlarged breast. Diffuse brawny induration of the skin of the breast with a peau-de-orange appearance usually without underlying palpable mass. The malignant cells forms tumor emboli invading dermal lymphatics results in blockage of lymphatics which are responsible for local signs and symptoms and distant

spread[21]. Primary IBC is not a specific histologic subtype of breast cancer but most often of the ductal type.

A needle biopsy usually establishes the histologic diagnosis of LABC. A full thickness skin biopsy is often obtained if IBC is suspected, as the hall mark of this disease is dermal lymphatic invasion. Once diagnosis is established, the following staging studies are generally recommended[22].

1. Complete history with physical examination
2. Bilateral mammography
3. Complete basic blood investigation
4. Chest radiography / CT, ultrasound
5. Pathology review and determination of ER, PR and HER –

   2 status

PROGNOSTIC FACTORS

Prognostic factors for locally advanced tumors are similar to the prognostic factors for earlier stage breast cancer includes age, menopausal status, tumor stage, histological grade, ER status and response to therapy [23.] Lymph node status and tumor size having the strongest effect on survival. The prognosis for patient with out lymph node metastasis is better than for those

patients with lymph node involvement and greater the number or higher nodal stage predict poor survival [24]. Breast tumors measuring <5cm, 5-10cm, >10cm associated with 5 year survival rates of 65%, 36% & 16% indicating the size of tumor also affects the survival rates[25]. Role of hormone receptor in LABC is less clear but studies found that ER and PR negativity was associated with shorter overall survival times [26] and hormone receptor positively is associated with longer survival time.

With above indicated prognostic factors, patients with axillary Lymphnode negative classified in 3 groups.

Low risk	**Moderate risk**	**High risk**
Tumor < 1 CMs	Turmor 1 – 2 cms	Tumor more than 2 cms.
Histology tubular, colloid		Histology - Comedo form
Papillary, less than 2 cms,		
ER / PR positive	ER / PR positive	ER / PR Negative
Nuclear Grade I	Nuclear grade II	Nuclear Grade-II, III
Age More than 35 years		Age-Less than 35 yrs

DNA Diploidy Over expression

Cathesin ‘D’

Low ‘S’ phase fraction. High ‘S’ phase fraction.

Other variables investigated as possible prognostic markers in locally advanced breast cancer includes HER2, P53,nuclear grade. P53 positivity was associated with shorter overall survival rate. .Her2 and nuclear grade have not consistently emerged as independent predictors of survival in multivariate analysis. Thymidine labeling index was a prognostic factor with a high TL1 predicting poorer survival [27]

Less common prognostic factors are

A. Proliferative indices like ki-67, PCNA/Cyclin, MIB-1

B. Topoisomerase II

C. Histone H3

D. Transforming growth factors (a,b)

E. Epidermal growth factor

F. Oncogene products (c-erb2,c-myc,ras, rb, Bcl2)

G. Invasion related proteins like Cathepsin-D, Laminin, Stromelysin, UPA/PA-1

H. Angiogenesis factors

I. PS2

J. NM- 23

K. Heat shock proteins

L. MDR -1 protein (multi drug resistant protein)

EVOLUTION OF THERAPY

According to National Cancer Institute' s surveillance Epidemiology and End Result program (SEER) the 3- and 5-year survival rates for woman with stage III breast cancer patients are 70% and 55% respectively and median survival is 4.9 years. Treatment for locally advanced breast carcinoma requires combination of systemic chemotherapy, surgery and radiotherapy to optimize the chance of cure. The earlier therapy for locally advanced carcinoma was radical mastectomy. However patient with chest wall fixation, skin edema, ulceration, presence of satellite nodules, inflammatory Breast carcinomas, matted (or) fixed lymph nodes, supraclavicular lymph nodes, or ipsilateral arm edema were all found to develop recurrences and these grave signs were considered as markers of inoperable disease[28] Patients were treated with primary radiotherapy also had risk of disease recurrence and death as well as the complication of chest wall fibrosis, Brachial plexopathy, lymphedema, skin ulceration and skin necrosis [29] Neo adjuvant chemotherapy was pioneered in the setting of locally advanced carcinoma in 1970 and major clinical responses to induction chemotherapy were noted in the

majority of patients and some were found to have no invasive tumour remaining within the breast or regional nodes at the time of surgery.

These data led to the hypothesis that the early locoregional response to neoadjuvant chemotherapy was a marker for response in distant occult micrometastases and that it could be used as a surrogate for the overall efficacy of the chemotherapy. Recently response to chemotherapy has allowed breast conserving therapy to become possible for woman who would otherwise have been eligible for mastectomy only and has substantially improved the prognosis of LABC patients.

The advantages of preoperative chemotherapy in LABC are

1. Chemotherapy administered prior of tumor removal is more biologically favorable than post operative administration [30].
2. Can reduce the size of the primary tumor render inoperable tumors resectable and sometimes even allowing for breast conserving surgery.

3. Permit a direct in vivo measure of the sensitivity of the tumor cells to the chemotherapeutic drug in that regimen,

4. Early identification of any resistance can prompt the change to a potentially more effective regimen[31]

5. Enable drug delivery through an intact tumor vasculature.

On the other hand the disadvantages are

1. Fewer than 5% of patients with LABC progress while undergoing neoadjuvant chemotherapy hence local treatment will be delayed.

2. Development of early drug resistance

3. May possibly increase the risk for surgical and radiation related complication but not proven [32]

In practice advantages of induction chemotherapy exceeds the disadvantages and this approach has become the standard treatment of care for woman with stage III breast cancer

CHOICE OF CHEMOTHERAPY REGIMEN

Most treatment guidelines recommend an initial Anthracyclin based regimen[33] Similar to the situation with

standard adjuvant chemotherapy, Anthracyclin and Cyclophosphamide (AC) most commonly with Flurouracil (FAC)regimen is used Other effective Anthracyclin based regimen includes Doxorubicin followed by CMF and intensive multidrug regimen. The recommended dose and schedule are the same as those used in the adjuvant therapy. Taxanes adds substantial efficacy to adjuvant chemotherapy and they are increasingly used for patients with node positive breast cancer. Trials are addressing the issues of induction regimens (i.e.) sequential Anthracyclin based chemotherapy followed by Taxanes are associated with twofold higher pathological complete response with better disease free survival and over all survival[34.] Taxanes are incorporated either as a cross over regimen follow (or) preceding Four cycles of Anthracyclin based regimen or as a component of an established Anthracyclin based regimen substituting for an existing older drug (eg Doxetaxal instead of flurouracil).

ROLE OF TRASTUZUMAB.

Trastuzumab is a monoclonal antibody that binds to a specific epitope of the HER-2/NEU protein. Approximately 20% of tumor breast cancers have amplified or over expressed HER-

2/neu (c-erB-2) a gene which encodes a cell surface growth factor receptor. Multiple doses can be given safety both alone and in combination with other chemotherapeutic agents.

Initial reports about Neoadjuvant Trastuzumab are encouraging but still be considered investigational at present since data on long term outcome and safety are lacking [35]

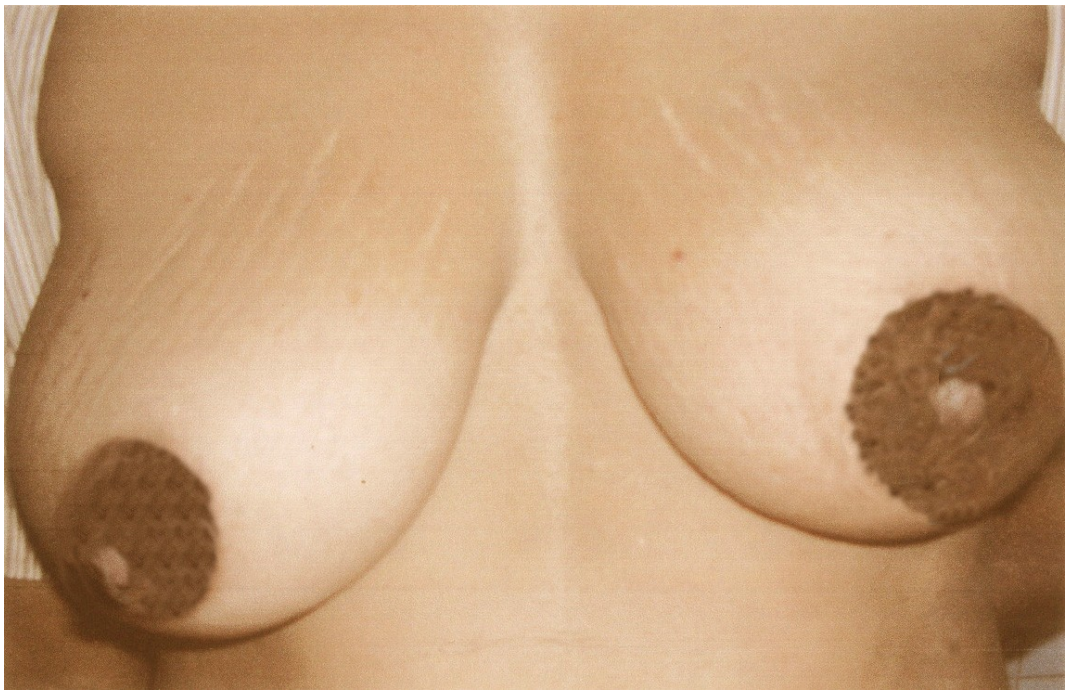
HIGH DOSE THERAPY WITH HEMATOPOIETIC STEM CELL SUPPORT

Main reason for treatment failure is lack of systemic control a fact that has led to the development of high dose chemotherapy regimen with autologous stem cell support and is indicated in progressive disease while receiving neoadjuvant chemotherapy and IBC. In general, higher objective and pathologic response rates have been obtained as a component of combined modality therapy, but there have been no dramatic improvements in either disease free survival or over all survival [36] and more over this approach is associated with markedly increased toxicity and worse quality of life compared to standard dose chemotherapy

DURATION OF NEOADJUVANT CHEMOTHERAPY

Optimal duration of induction chemotherapy has not been established in randomized controlled trials. Based on various results, 2003 consensus conference on neoadjuvant chemotherapy for breast cancer recommended the following approach to induction therapy [37].

- Four cycles of an anthracyclin based regimen or a taxanes followed by reassessment of response.
- If there has been a complete or nearly complete clinical response to induction therapy definite local treatment is appropriate.
- Patients with a lesser response could be considered for additional cycles of a non cross resistant drugs.
- Eight total cycles of adjuvant therapy are recommended. They may all administered preoperatively (or) split between induction and postoperative therapy.



PRIMARY TUMOUR BEFORE NEO ADJUVANT CHEMO THERAPHY WITH ELEVATED AND RETRACTED NIPPLE

REGRESSED PRIMARY TUMOUR AFTER NEO ADJUVANT CHEMO THERAPHY

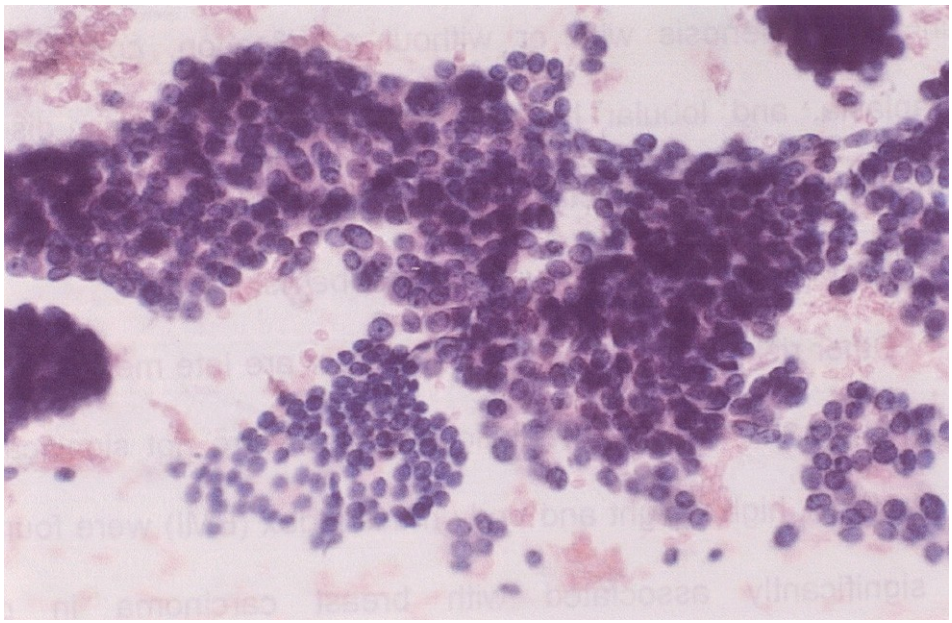
- In the absence of progressive disease atleast two or preferably four cycles should be given before concluding patients as Non responders.

RESPONSE TO NEOADJUVANT THERAPY

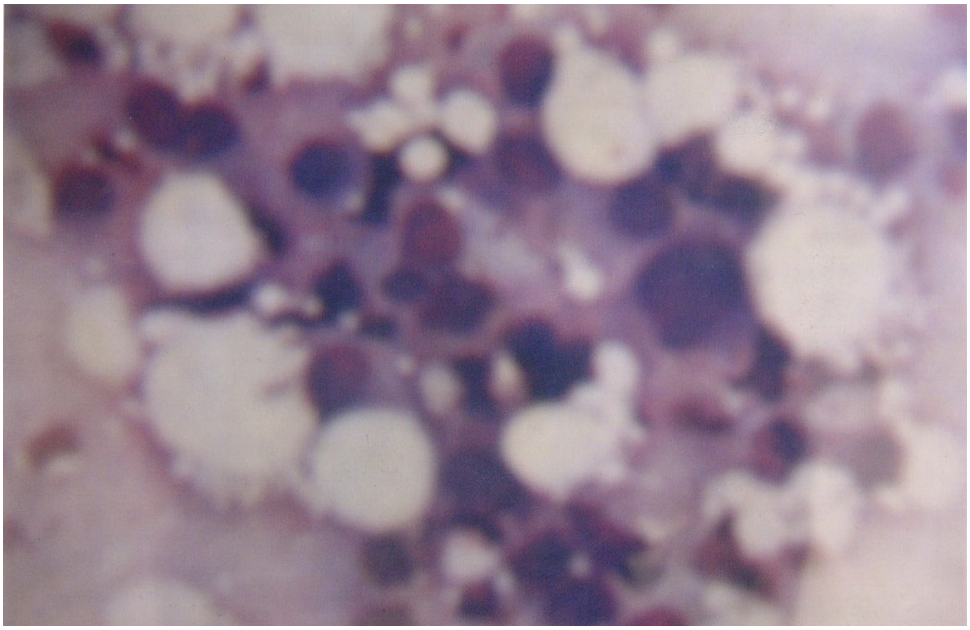
Clinical measurements of breast masses are often used to assess the response to neoadjuvant chemotherapy. Universally accepted criteria for response to Neoadjuvant chemotherapy are classified by the world health organizations / international union against cancer (WHO/UICC) that have been used for 20 year defines

A clinical complete response (CCR) as complete disappearance of all clinically detectable disease in the breast or regional lymph node (41). A partial response (PR) requires a >50% reduction in the sum of the product of two largest dimensions of measurable tumor. <50% reduction in the sum of the product of two largest dimensions of measurable tumor Minor responders Non responders(NR) as there no change in clinical status. Progressive disease includes >25% increase in sum of product of two largest perpendicular dimension of the tumor[38]

Same clinician should perform longitudinal assessment of chemotherapy response although mammography and ultrasound are of limited value for monitoring response to neoadjuvant therapy. None of



FNAC PICTURE OF PRIMARY TUMOUR BEFORE NEO ADJUVANT CHEMO THERAPHY



HISTO PATHOLOGY PICTURE OF PRIMARY TUMOUR AFTER NEO ADJUVANT CHEMO THERAPHY SHOWING CYTOPLASMIC VACOULISATION

the additional imaging modality such as MRI, Helical CT, even PET scans are routinely used for response assessment[39]

Based on histological response to neoadjuvant chemotherapy such as cytoplasmic vacuolization, change in mitosis, tumour sclerosis in the primary tumor and the presence of nodal fibrosis mucin pools or large aggregates of foamy histiocytes in the lymph node(1b), Pathological complete response was characterized as when there is no evidence of residual invasive tumor in the Breast or axillary lymph nodes. Partial pathological response is either residual non invasive tumor (or) microscopic foci of tumor cells of more or less than 1cm3. Pathological lack of response is confirmed by comparing tumor size measurement of surgical specimen with clinical size measurements [40]

MOLECULAR PREDICTORS OF RESPONSE

Many investigations studied about markers that predict response to chemotherapy for patient treated with anthracyclin based induction chemotherapy, high nuclear grade, high proliferative index (K167) and co expression of HER2/neu and topoisomerase II have been associated with greater response rate [41]. Conversely mutation of the P53 gene is associated with

a lower response rate to chemotherapy[42] and tumors with low level of HER-2 expressions are more likely to respond to concomitant paclitaxal therapy[43] Since response to chemotherapy is an important predictor of survival, studies about predictors are too preliminary at this point to be used in clinical setting since sufficient data are lacking.

NEOADJUVANT HORMONE THERAPY : NAHT

It is an acceptable option for selected patients with Estrogen receptor positive Breast cancer although the likelihood of complete pathologic response appears to be lower than with systemic therapy [44]

Tamoxifen :

Neoadjuvant tamoxifen decreases overall tumor volume in approximately one half of LABC and pathological complete response appears to be low about approximately 5% Since response tend to occur gradually, treatment for 3-6 months is necessary in the absence of progression before concluding that disease is unresponsive

Aromatase Inhibitors

With Aromatase Inhibitors the medium reduction in tumor volume over 12 weeks was 70 to 80% in ER positive locally

advanced breast Cancer patients[45] and in woman whose tumor expresses HER 2/neu and erbB-1 may preferentially benefit from NAHT with Aromatase Inhibitors compared to Tamoxifen.

NAHT is an effective approach for woman with LABC but may be reserved for elderly woman with impaired organ function, patient who are unwilling to accept chemotherapy related toxicity or those with poor performance status or who are felt to have unacceptably high surgical risk

INDUCTION CHEMORADIATION

Concurrent radiation therapy and chemotherapy has only rarely been applied to patients with LABC because of concerns about radiosensization with anthracyclins. The efficacy has prompted a revolution of the benefits of initial chemotherapy [46] As long term results are not yet available, this treatment approach is still under study.

LOCAL THERAPY

Following induction chemotherapy, the options for local therapy are surgery(Mastectomy) or RT or both. In general, assessment of tumor response after induction chemotherapy usually drives loco regional management recommendations. The risk of locoregional recurrence in woman with LABC who

are treated with surgery or RT alone is approximately 30 to 50 present and the most studies that have compared primary radiation therapy with primary surgical therapy have shown equivalent outcome [47] But postoperative RT had significantly lower rate of 10 year loco regional recurrence and cause specific survival was also significantly better for these with Stage III B disease, Clinical T4 tumors, or ≥ 4 positive nodes [48] Indications for locoregional RT is controversial but in selective cases.

Indications for post op RT includes:

1. tumour size more than 5cms diameter
2. intensive pectoral muscle involvement
3. positive surgical margins
4. >4 positive axillary lymph nodes
5. gross extracapsular tumor extension.

Hence local control rates appear higher when both surgery and RT are included in the treatment strategy even for woman who have partial clinical response to neoadjuvant chemotherapy.

BREAST CONSERVING THERAPY AFTER NEOADJUVANT CHEMOTHERAPY(BCT) :

50-90% of woman with LABC can be successfully treated with Breast Conserving surgical Therapy (BCT) after Neoadjuvant chemotherapy but not appropriate for all women even if they appear to have achieved major clinical response. Recommended eligible criteria for BCT in women with LABC are presented in Table [49]

Eligibility Criteria for Breast Conservation Therapy After Induction Chemotherapy in LABC

Ineligible	Eligible
T4 lesions	T3 lesions
Progression or no response to systemic chemotherapy	Dramatic tumor shrinkage
Excisional biopsy of the residual nidus produces an unacceptable cosmetic outcome	Small or residual nidus which can be excised with acceptable cosmesis
Excisional biopsy reveals extensive residual tumor or islands of tumor throughout the specimen or positive margins	Minimal or no microscopic tumor with negative surgical inked margins
Multicentric tumors	Unicentric tumor
Extensive microcalcifications associated with an extensive intraductal component documented to persist post chemotherapy	Invasive cancer without extensive intraductal carcinoma throughout the quadrant or beyond
Small breast where excision of residual nidus produces an unacceptable cosmetic outcome	Small residual nidus in a large breast
Systemic lupus erythematosis, scleroderma, or active dermatomyositis (relative contraindications)	No connective tissue disease

LABC: locally advanced breast cancer

A prognostic index to estimate the likelihood of an in breast or loco regional tumor recurrence was developed in patients undergoing BCT after Neoadjuvant Chemotherapy[50]

Unfavorable characteristic are

- Clinical N2 or N3 disease
- Residual pathologic tumor size >2cm
- Multifocal residual disease
- Lymphovascular space invasion

Five year survival rate of an in breast recurrence free survival rate decreases when more than two of these unfavorable characteristics present. If Breast conservative therapy is contemplated, special attention to be paid to the tumors localization before starting Neoadjuvant Chemotherapy so that original tumor site can be located if a complete CR is achieved to neoadjuvant chemotherapy. This can be accomplished by inserting radio opaque clip into the central portion of the tumour under the guidance of ultrasound prior to neoadjuvant chemotherapy BCT is generally not considered as an appropriate option for women with inflammatory breast cancer.

AXILLARY STAGING

Regional Lymph Nodal Status impacts prognosis and choice of therapy. Majority of LABC patients presents with

palpable nodal disease and in some cases advanced (N2, N3). Minority of patients who are clinically node negative, assessment of locoregional nodal status is often considered prior to therapy. Sentinel lymphnode mapping (SLN) and Biopsy has been integerated into the care of early breast cancer patients with T1, T2 Breast tumor <5cm and T3 with clinically node Negative tumor [51] The prognostic information obtained by axillary staging after neoadjuvant chemotherapy is equivalent or superior to that gained prior to systemic therapy since it permits an assessment of response to neoadjuvant chemotherapy.

American Society of Clinical Oncology (ASCO)Guidelines suggest that if prognostic information gained from examination of the axillary nodes is considered valuable for planning local regional treatment for an individual patient, SLNB can be considered before the institution of systemic therapy in clinically node negative patients

Prognosis of LABC Based Upon Pathologic Response and Nodal Status†

Number of positive LN following neoadjuvant chemotherapy	Five year survival, percent
Pathologically negative	75
0-4 + LN	40-50
5-10 + LN	30
>10 + LN	20

† Data from Buzdar, AU. Surg Oncol Clin North Am 1995; 4:715.

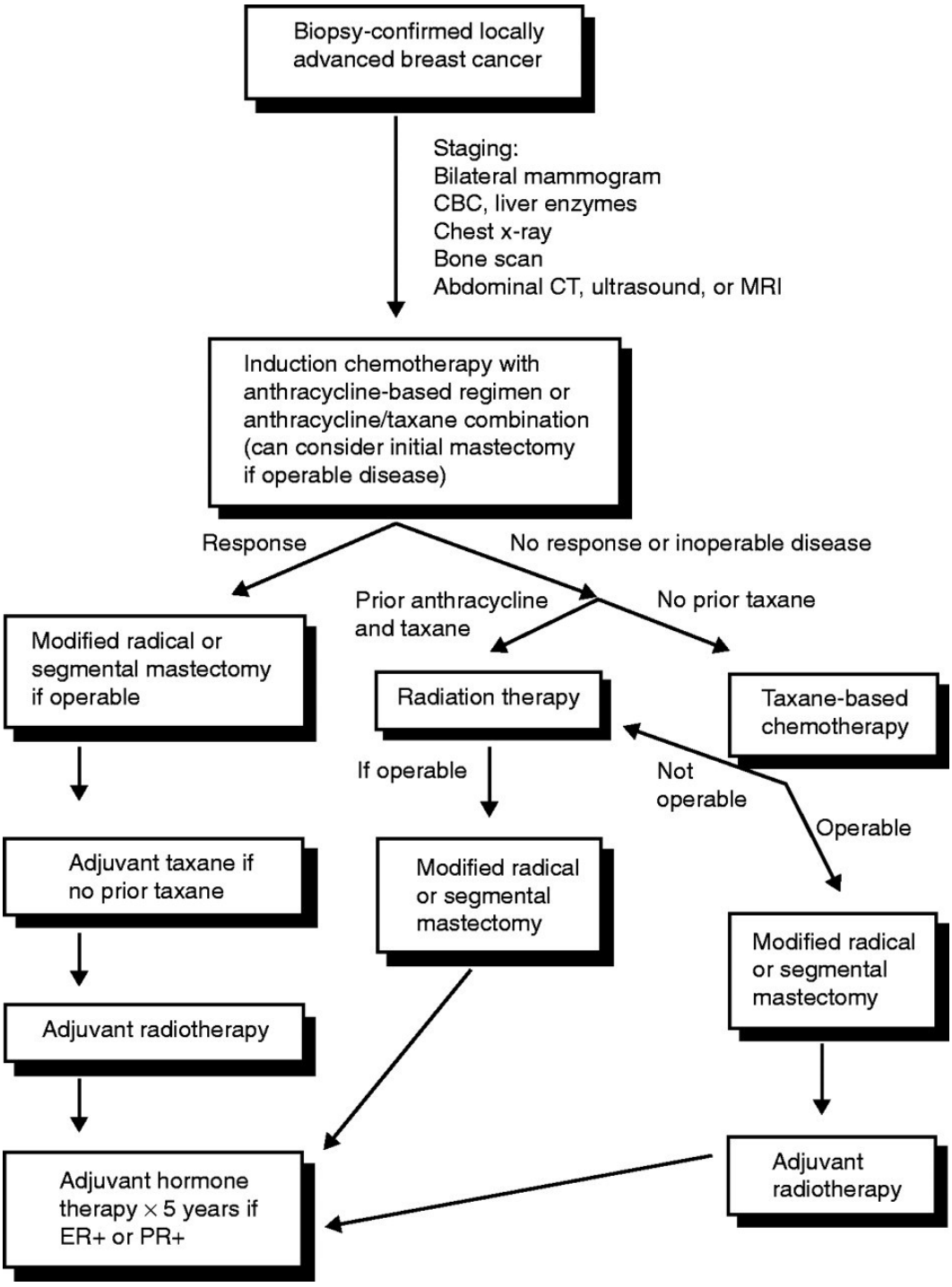
If SLN is negative, axillary lymph node dissection is not preformed at the time of surgery, instead the axilla is irradiated. If the SLN is positive, an axillary lymph node dissection is done at the time of surgery and the axilla and supraclavicular nodes are irradiated only if the nodes are persistently positive .

MANAGEMENT OF NON RESPONDERS

Failure to respond to neoadjuvant chemotherapy is a poor prognostic sign particularly if disease progresses during therapy. Approximately 1/3rd remain free of distant disease with multidisciplinary locoregional management [52] surgery should only be attempted if macroscopically complete resection can be

accomplished. Patients who remain inoperable should receive loco regional RT with subsequent surgery if feasible [53] Chemotherapy with a non cross resistant regimen is preferred option (Taxanes in women who progress during Anthracyclins based therapy. Hormone therapy is appropriate for patient whom tumors are ER positive.

Treatment algorithm for locally advanced breast cancer.



PATIENTS AND METHODS

Out of all Breast Cancer patients who attends surgical out patient department, 39 patients who presented with locally advanced breast cancer patients 30 patients were enrolled in our study. Each patient was examined to confirm the diagnosis of LABC and to evaluate the clinical stage of the disease at presentation and the response to chemotherapy. The staging work up included a complete history, physical examination, complete blood cell count, blood chemical analysis, ECG, chest radiograph, abdominal ultrasound and diagnosis established with fine needle aspiration biopsy from the tumor and involved axillary lymph nodes.

Four cycles of induction chemotherapy was administered at 18-21 days interval. The regimen (AC regimen) used were Inj. Adriamycin 50-60mgm/m^2 and Inj. Cyclophosphamide 600-900 mgm/m^2 as 24 hrs continuous IV infusion on the day 1. Clinical responses and examinations was done on every visit for induction chemotherapy.

All patient underwent modified radical mastectomy with axillary dissection after completing 4 cycles of neoadjuvant

chemotherapy within a period of 3 weeks and the clinical and pathological response to the induction chemotherapy was evaluated. These included section from each quadrants and the nipple areolar complex.

Postoperatively patients received four more cycles of AC and during each follow up, patient had a history and physical examination, complete blood count, LFT, serum Calcium ,and if the patients symptomatic or suspicious , chest X-ray X ray spine or long bones. USG abdomen done every 2 months.

9 patients were excluded from the study because one patient died before surgery, Two patients defaulted due to intolerance to chemotherapy and 1 patient withdrawn due to development of malignant pleural effusion during the course or induction chemotherapy. 2 patients violation in the regularity of chemotherapy cycles and 3 didn't turned out for follow up after surgery..

Data were analyzed using mean and standard deviation. Paired t-test was used to compare the reduction in tumor size and regression in number of axillary lymph node metastasis. Life table and Kaplan meier methods were used to estimate the

disease free survival ship. Data were analysed using SSPS (11.5version).

Table.1. Age at Presentation

Study group	Number of patients	Percentage
40-49	9	30%
50-59	15	50%
>60	6	20%

In our study group patients ranges from 40-65 yrs and the median age is 52 yrs. Maximum number of patients were in the range of 50-60 yrs.

CHART.1

AGE AT PRESENTATION

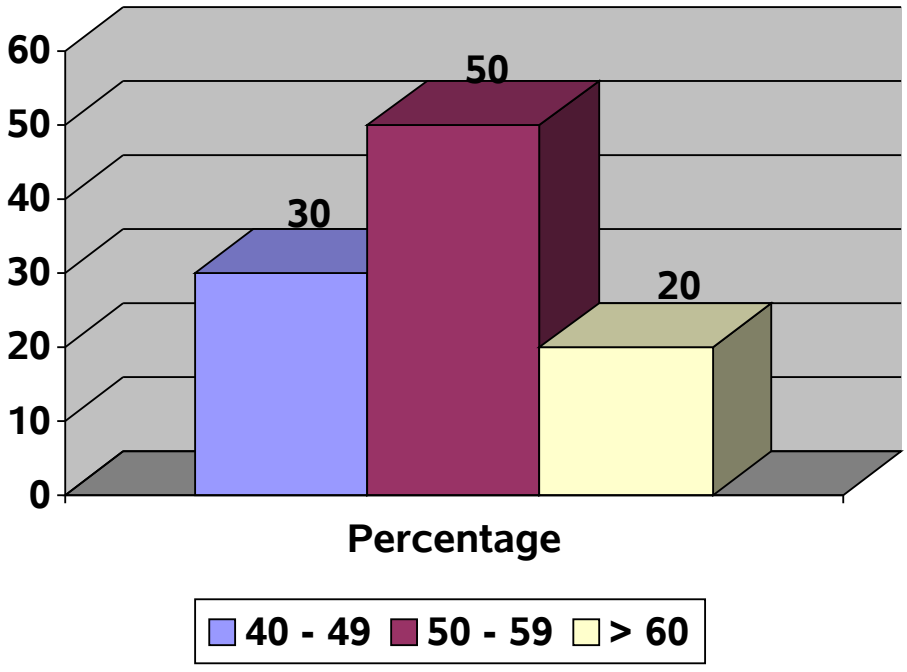


Table 2.Menopausal Status

Study Group	Number of patients	Percentage
Pre-menopausal	9	30%
Post-menopausal	21	70%

CHART.2

MENOPAUSAL STATUS

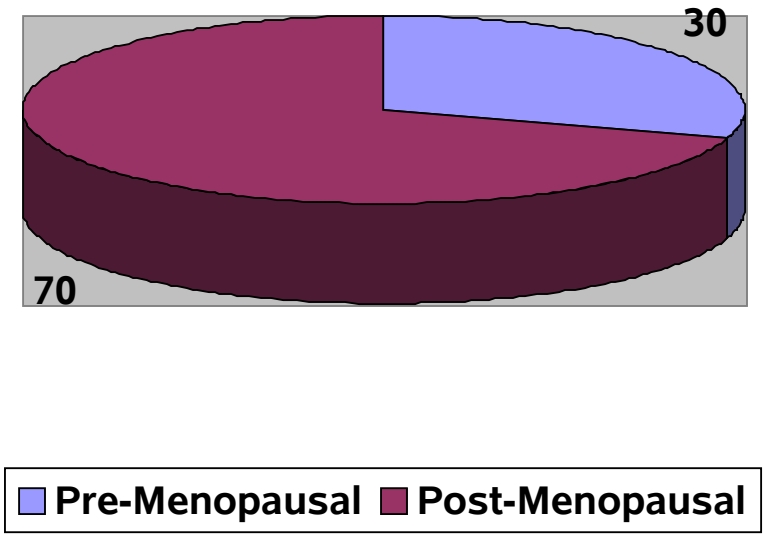


Table.3.Side and quadrant of breast lesion

Quadrant with side	Number of patients
RUO	8
RLO	3
RUI	4
RLI	1
CENTRAL	2
LUO	5
LLO	2
LUI	2
LLI	1
CENTRAL	2

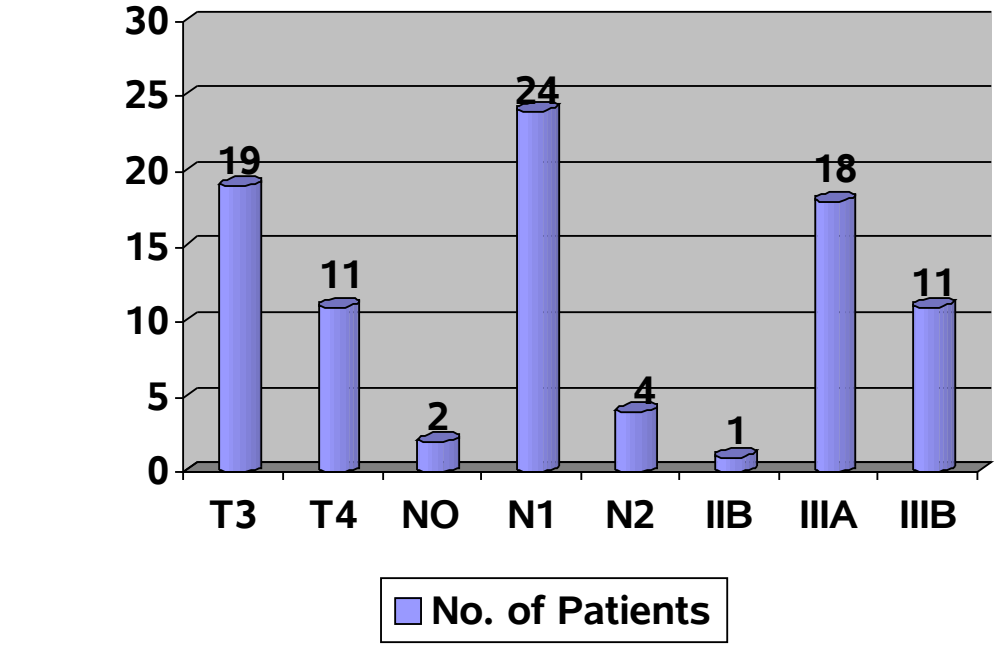
In our study group most of the patient post menopausal and upper outer quadrant is the most common site of index lesion.

Table 4 lists the clinical characteristics for the 30 assessable pretreatment patients. Most of the patients in our study groups were presented with stage III with 60% stage IIIA and 39% with stage IIIB patients. 80% of locally advanced breast cancer patients showed N1 disease in our study group. The mean tumor size is 7.96cms and the no of lymph nodes is 4.26.

CHART.3

CLINICAL CHARACTERISTICS OF

THE PRETREATMENT PATIENTS



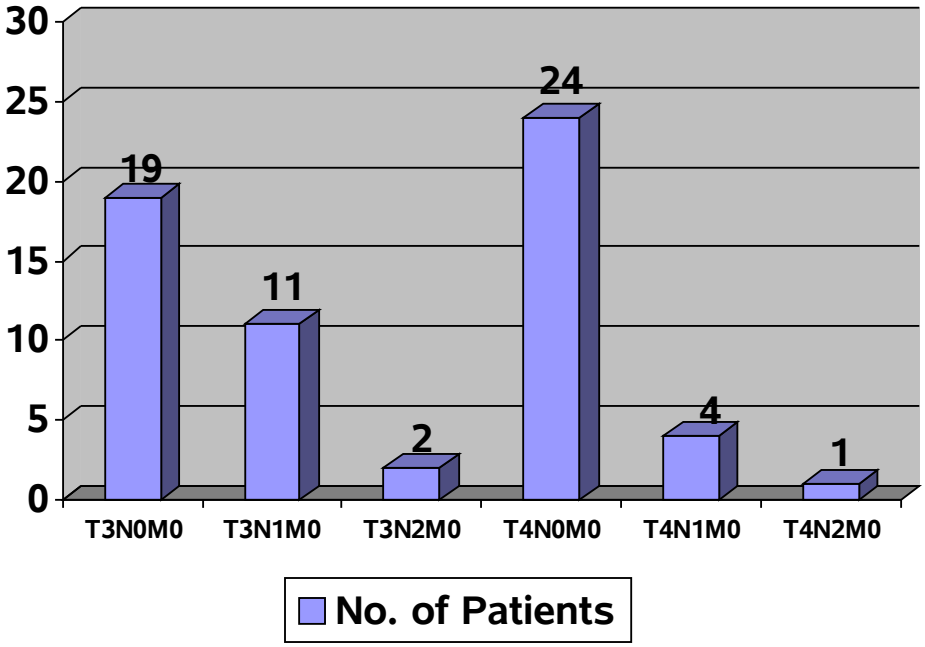
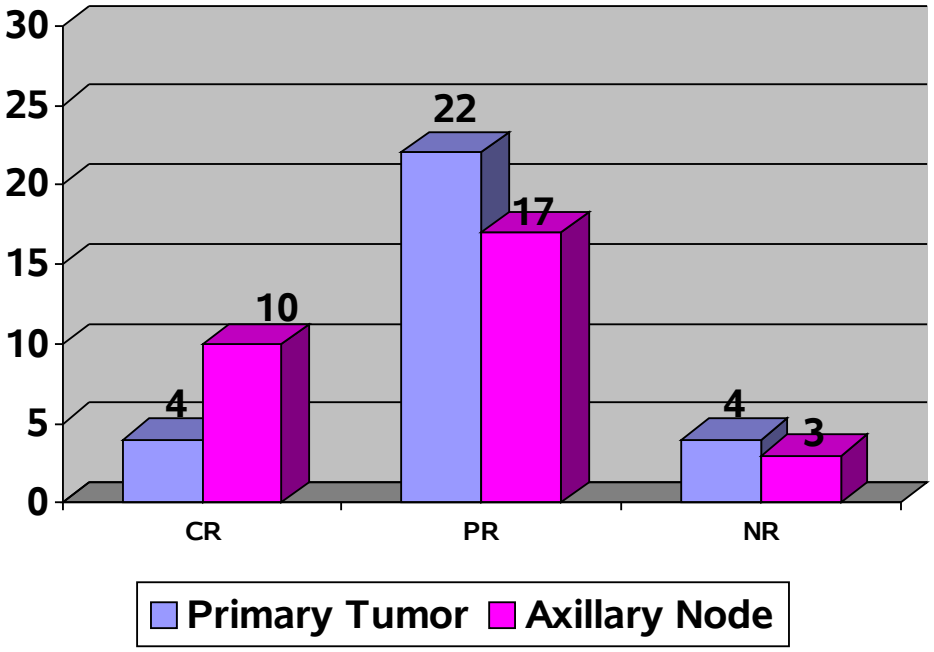


Table 4. clinical characteristics of the pretreatment patients

Characteristics of the patients.	No of patients
Initial tumor size	
T3	19
T4	11
Initial nodal status	
N0	2
N1	24
N2	4
Initial stage	
II B	1
IIIA	18
IIIB	11
T3N0M0	1
T3N1M0	16
T3N2M0	2
T4N0M0	1
T4N1M0	8
T4N2M0	2

CHART.4

Pathologic findings in breast and axillary specimen in response to chemotherapy


30
25
20
15
10
5
0
22
17
10
4
4
3
CR
PR
NR
Primary Tumor
Axillary Node

The clinicopathological responses in breast and axillary lymph nodes to induction chemotherapy was analyzed with respect to the initial tumor and lymph nodal status and was shown in the tabular column.

Table.5.Pathologic findings in breast and axillary specimen in response to chemotherapy

Primary tumor	No. Patients	(%)
Complete response (no residual invasive disease;)	4	13.3
Partial response (≥50% decrease in primary tumor size)	18	73.4
(<50% decrease in primary tumor size)	4	
No response/stable disease	4	13.4
Axillary nodal findings		
Complete response	10	33.4
Partial response	17	56.6
No response	3	10

13% of patients showed complete primary tumor response and 73% of patients showed partial response to induction chemotherapy. 34% of patients showed complete axillary nodal regression and 10% showed no response in our study. Statistically analysis of data on tumor size and number of

axillary lymph nodes before and after administration of induction chemotherapy has shown in the table

Table.6.Statistically analysis

	Pre neoadj.		Post neoadj.			
	mean	SD	mean	SD	T	p.value
Tumor size	7.96cm	1.51	3.26cm	2.46	12.96	0.00
Nodal status	4.26	0.98	1.80cm	1.73	10.79	0.00

Relationship between the pathological primary tumour response and axillary lymph nodal were evaluated and the results are shown in the Table.

Table.7.Relationship Between Pathologic Primary Tumor Response and Axillary Lymph Node Status After Neoadjuvant Chemotherapy*

		Metastatic Axillary Lymph Nodes						
		0		1-3		≥4		
Primary Tumor		No.	%	No.	%	No.	%	*P*
Complete response	pathologic	3	75	1	25	0	0	< .01

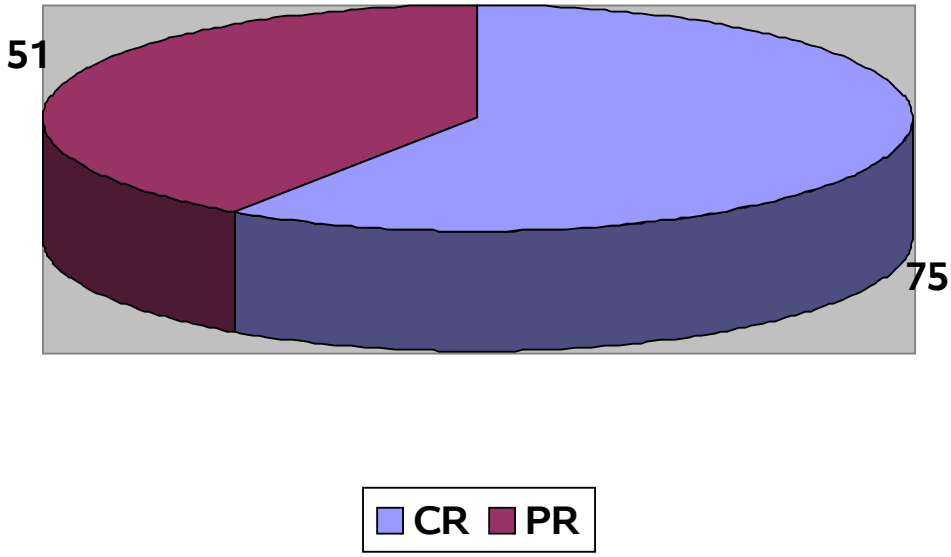
Incomplete response/no response	pathologic	7	26.9	9	34.6	10	38.5

Table.8. Relationship of pathological primary tumor and axillary lymph node response to disease free survival after Neoadjuvant therapy.

Pathological response	No. of Patients Developed recurrence	Recurrence Rate	Disease free survival rate
Patients with Complete response	1	25%	75%
Patients with Partial response	9	49%	51%

CHART.5

Relationship of pathological primary tumor and axillary lymph node response to disease free survival after Neoadjuvant therapy



Out of 4 patients who had complete pathological primary tumor response 3 patients had no axillary lymph nodal metastasis after induction therapy when compared to 7 patients out of 26 patients who had incomplete pathological primary tumor response. At a median follow up of 21 months (ranges from 12 months to 36 months) among the patient who had complete pathological response there was 1 patient with locoregional recurrence in contrast among the patients who showed incomplete pathological responses 8 patients had locoregional recurrences and one patients developed malignant pleural effusion Relationship between pathological primary tumour and axillary lymph nodal response to disease free survival after neoadjuvant chemotherapy was analysed and shown in the table.

The site of locoregional recurrence in both complete and incomplete response were shown in the tabular column.

Study group	Site				Total no of patients
	Scar	Tumour bed	Axilla	Distant met.	

Complete response	1	-	-	-	1
Incomplete response	3	2	3	1	9

RECURRENT CARCINOMA AT THE SCAR SITE

RECURRENT AXILLARY LYMPHNODE METASTASIS WITH ARM EDEMA

DISCUSSION

Nowadays locally advanced breast carcinomas are commonly treated with neoadjuvant chemotherapy followed by definitive surgery. The results of our study indicates that in many patients, neoadjuvant chemotherapy can completely clear the breast and axillary lymph nodes of any microscopic evidence of invasive tumor as assessed by standard histologic examination. In our study group this occurred in 4patients (13% of patients) after four cycles of AC regimen with over all clinical responses to induction therapy in 80% of patients. Powels et al and Kuerer et all shown similar results in 10% and !6% of locally advanced breast carcinoma patients with Anthracyclin based Neoadjuvant chemotherapy. Sataloff et al shown similar results with 39% of patients with complete clinical response with overall clinical responses to induction therapy in 86% and experienced significant shrinkage of primary tumor there by facilitating subsequent surgery.

The study has also been shown that the induction chemotherapy convert clinically involved axillary nodal disease to a pathological negative status in 10 patients (34%). 2 different studies Hortobagi et al and Fisher et al shown similar

response rate of primary tumor and lymph nodes in about 35% to 40% of locally advanced breast cancer patients.

One major goal of systemic therapy in the early eradication of subclinical distant micrometastasis in an attempt to improve survival. Theoretically one could surmise that the response of axillary lymph node metastasis to systemic therapy might reflect the sensitivity of occult metastasis in the other organ compartments.

In our study of relationship between the pathological primary tumour response and axillary lymph nodal response were evaluated and the results shown that a pathological complete primary tumor response were more likely to have negative axillary lymph node status.75% of patients(n=3 out of 4) had no axillary lymph node metastasis when compared to 27% (n=7 out of 26)of patients with pathological incomplete primary tumor response which is statistically significant. Kuerer et al had similar results in which 73% of patients had no axillary metastasis in pathologically complete response with improvement in overall and disease free survival. Hyytinen et al

and Teixeira et al also shown similar results in their series of studies.

Results of our study also shows that the patients with complete pathological response in primary tumor and axillary lymphnode had significant fewer recurrence (n=1) 25% than did the patients with an incomplete response (n=9)49%. and significant higher disease free survival 75% than the patients with an incomplete response 51% and the p value for both is <0.01. NSABP B-18 and other trials has shown similar results and conclusively proven better disease free survival rates and over all survival rates in pathological complete primary tumor response and axillary lymphnode in 80-85% of patients than patients with an incomplete response to neoadjuvant chemotherapy ranges from 55-65% .

In our study the follow up period was only 3 years with median follow up period of 21 months and probably 5 years disease free survival and overall survival rates may be on par with this short study and it is too early to comment on it.

SUMMARY

Neoadjuvant chemotherapy totally eradicated the histologic evidence of invasive cancer in both the primary breast tumor and axillary lymphnode in approximately 13% of locally advanced breast carcinoma patients who receive 4 cycles of induction chemotherapy with overall response in about 80% of the patients.

Patients with complete pathological primary tumor response were more likely to have no axillary lymph node metastasis in 75% of patients compared with the patients having partial pathological response in the primary tumor after induction chemotherapy.

Patients with complete pathological response in both primary tumor and axillary lymph nodes had decreased recurrence rate with significant improved disease free survival when compared to the patients with partial pathological response

CONCLUSION

The results from our study suggest that the maximal tumor shrinkage and sterilization of potentially involved axillary lymph nodes after the induction chemotherapy in locally advanced breast cancer patients rendered surgically resectable in most number of patients.. Our studies also shown that complete regression in number of metastatic lymph nodes in complete pathological primary tumor response associated with eradication of distant occult metastasis which is an important prognostic factor and shows significant improvement in disease free survival of breast cancer patients. The above result suggest that Neoadjuvant chemotherapy is the standard management in patients with locally advanced breast carcinoma. But prediction of response to induction chemotherapy in breast cancers remains to be determined and many studies recently focused on potential biological markers which influence the response to induction chemotherapy.

BIBLIOGRAPHY

1. Hortobagyi, GN, Sinigletary, SE, Strom, EA. Treatment of locally advanced and inflammatory breast cancer. In: Diseases of the Breast, Harris, JR, Lippman, ME, Morrow, M, Osborne, CK (Eds) 2nd Ed, Lippincott Williams and Wilkins, Philadelphia 2000.

2. Rubens, RD, Bartelink, H, Engelsman, E, et al. Locally advanced breast cancer: the contribution of cytotoxic and endocrine treatment to radiotherapy. An EORTC Breast Cancer Co-operative Group Trial (10792). Eur J Cancer Clin Oncol 1989; 25:667.

3. Swain, SM, Sorace, RA, Bagley, CS, et al. Neoadjuvant chemotherapy in the combined modality approach of locally advanced nonmetastatic breast cancer. Cancer Res 1987; 47:3889.

4. Shenkier, T, Weir, L, Levine, M, et al. Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer. CMAJ 2004; 170:983.

5. Bailey and love. Short practice of surgery 24th edition The breast.pg.no.824.

6. Schwartz .principle of surgery 7th edition vol.1 Anatomy of breast. pg no 334.

7. Nyhus. mastery of surgery 4th edition vol.1 Anatomy of breast. Pg.no.565.

8. LIndholm K : Cytology versus histology in carcinoma in situ of the breast and the role of fine needle aspiration cytology in treatment of carcinoma in situ : In : Goerttler K, Feichter GE, Write S (eds) New frontiers in cytology. Modern aspects of research and practice. Springer, Berlin 1988.

9. Sneige N, Zacharia IJ, Fannin TV, Dekmezian RH, Ordornez NG : Dine needle aspiration cylology of metastatic neoplasma in the breast. Am J Clin Patho 192 37-35, 1989.

10. Naran S, Simpson J, Gupta R : Cytologic diagnosi of papillary carcinoma of the breast in needle aspirates, Diagn Cytopathaol 4 : 33-37, 1988.

11. Salhany KR, Page DL : fine – Needle aspiration of mammary lobular carcinoma in situ and atypical lobular hyperplasia. Am, J, (Clin Pathol 92 : 22-26, 1989)

12. Kern WH : The diagnosis of breast cancer by fine needle aspiration smears JAMA 241 : 1 12_5-1, 1979.

13. Bondeson K : Aspiration cytology of radiation – induced changes of mormal breast epithelium. Acta 31 : 309-310, 1987.

14. rupp M, Hafiz MA, Khalluf E, Sutula M : Fine needle aspiration in stormal sarcoma of the breast. Light and electron microscopic findings with histologic correlation. Acta Cytol 32 : 72-74, 1988.

15. Masin M, N Masin F : cytology of angiosarcoma of the breast. A case report. Acta Cytol 22 : 162-164, 1978.

16.Cuschieri. Essential of surgical practice 4th edition. Disorders of breast. Pg.no.69.

17. AJCC Cancer Staging Manual, 6th ed, Greene, FL, Page, DL, Fleming, ID, et al (Eds), Springer-Verlag, New York 2002. p.223.

18. Robbins, GF, Shah, J, Rosen, P, et al. Inflammatory carcinoma of the breast. Surg Clin North Am 1974; 54:801.

19. Hance, KW, Anderson, WF, Devesa, SS, et al. Trends in inflammatory breast carcinoma incidence and survival: the

surveillance, epidemiology, and end results program at the National Cancer Institute. J Natl Cancer Inst 2005; 97:966.

20. Jacquillat, C, Baillet, F, Weil, M, et al. Results of a conservative treatment combining induction (neoadjuvant) and consolidation chemotherapy, hormonotherapy, and external and interstitial irradiation in 98 patients with locally advanced breast cancer (IIIA-IIIB). Cancer 1988; 61:1977.

21. Jaiyesimi, IA, Buzdar, AU, Hortobagyi, GN. Inflammatory breast cancer: a review. J Clin Oncol 1992; 10:1014.

22. National Comprehensive Cancer Network (NCCN) guidelines for treatment of breast cancer. Available at www.nccn.org/professionals/physician_gls/default.asp (Accessed March 7, 2005).

23. Scholl, SM, Fourquet, A, Asselain, B, et al. Neoadjuvant versus adjuvant chemotherapy in premenopausal patients with tumours considered too large for breast conserving surgery: preliminary results of a randomised trial: S6. Eur J Cancer 1994; 30A:645.

24. Toonkel LM, Fix I, Jacobson LH et al. Locally advanced breast carcinoma: results with combined regional therapy. Int J Radiat Oncol Biol Phys 1986;12:1583–1587.

25. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 1989;63:181–187.

26. Bonnefoi H, Diebold-Berger S, Therasse P et al. Locally advanced/inflammatory breast cancers treated with intensive epirubicin-based neoadjuvant chemotherapy: are there molecular markers in the primary tumour that predict for 5-year clinical outcome? Ann Oncol 2003;14:406–413

27. Ozmen V, Cabioglu N, Dolay K et al. Biological considerations in locally advanced breast cancer treated with anthracycline-based neoadjuvant chemotherapy: thymidine

labelling index is an independent indicator of clinical outcome. Breast Cancer Res Treat 2001;68:147–157

28.. Haagenson, CD, Stout, AP. Carcinoma of the breast. Criteria of inoperability. Am Surg 1943; 118:859.

29. Spanos WJ Jr, Montague ED, Fletcher GH. Late complications of radiation only for advanced breast cancer. Int J Radiat Oncol Biol Phys 1980;6:1473–1476.

30. Fisher, B, Gunduz, N, Saffer, EA. Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases. Cancer Res 1983; 43:1488

31. Thomas, E, Holmes, FA, Smith, TL, et al. The use of alternate, non-cross-resistant adjuvant chemotherapy on the basis of pathologic response to a neoadjuvant doxorubicin-based regimen in women with operable breast cancer: long-term results from a prospective randomized trial. J Clin Oncol 2004; 22:2294.

32. Graham, MV, Perez, CA, Kuske, RR, et al. Locally advanced (noninflammatory) carcinoma of the breast: results and comparison of various treatment modalities. Int J Radiat Oncol Biol Phys 1991; 21:311.

33. Kaufmann, M, von Minckwitz, G, Smith, R, et al. International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. J Clin Oncol 2003; 21:2600.

34. Smith, IC, Heys, SD, Hutcheon, AW, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol 2002; 20:1456.

35. Burstein, HJ, Harris, LN, Gelman, R, et al. Preoperative Therapy With Trastuzumab and Paclitaxel Followed by Sequential Adjuvant Doxorubicin/Cyclophosphamide for HER2 Overexpressing Stage II or III Breast Cancer: A Pilot Study. J Clin Oncol 2003; 21:46.

36. Chevallier, B, Bastit, P, Graic, Y, et al. The Centre H. Becquerel studies in inflammatory non metastatic breast cancer. Combined modality approach in 178 patients. Br J Cancer 1993; 67:594.

37. Schwartz, GF, Hortobagyi, GN. Proceedings of the consensus conference on neoadjuvant chemotherapy in carcinoma of the breast, April 26-28, 2003, Philadelphia, Pennsylvania. Cancer 2004; 100:2512.

38. Hayward, JL, Carbone, PP, Heuson, JC, et al. Assessment of response to therapy in advanced breast cancer: a project of the Programme on Clinical Oncology of the International Union Against Cancer, Geneva, Switzerland. Cancer 1977; 39:1289.

39. Herrada, J, Iyer, RB, Atkinson, EN, et al. Relative value of physical examination, mammography, and breast sonography in evaluating the size of the primary tumor and regional lymph node metastases in women receiving neoadjuvant chemotherapy for locally advanced breast carcinoma. Clin Cancer Res 1997; 3:1565.

40. Feldman LD, Hortobagyi, GN, Blumensaien G.R. Pathologic assessment of response to induction chemotherapy in breast cancer. Cancer res.1986;46: 2578-2581.

41.Park K, Kim J, Lim S et al. Topoisomerase II-alpha (topoII) and HER2 amplification in breast cancers and response to preoperative doxorubicin chemotherapy. Eur J Cancer 2003;39:631–634.

42. Anelli A, Brentani RR, Gadelha AP et al. Correlation of p53 status with outcome of neoadjuvant chemotherapy using paclitaxel and doxorubicin in stage IIIB breast cancer. Ann Oncol 2003;14:428–432.

43. Kuerer HM, Newman LA, Smith TL et al. Clinical course of breast cancer patients with complete pathologic primary tumor

and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol 1999;17:460–469

44. Hoff, PM, Valero, V, Buzdar, AU, et al. Combined modality treatment of locally advanced breast carcinoma in elderly patients or patients with severe comorbid conditions using tamoxifen as the primary therapy. Cancer 2000; 88:2054.

45. Brito, RA, Valero, V, Buzdar, AU, et al. Long-term results of combined-modality therapy for locally advanced breast cancer with ipsilateral supraclavicular metastases: The University of Texas M.D. Anderson Cancer Center experience. J Clin Oncol 2001; 19:628.

46. Formenti, SC, Volm, M, Skinner, KA, et al. Preoperative Twice-Weekly Paclitaxel With Concurrent Radiation Therapy Followed by Surgery and Postoperative Doxorubicin-Based Chemotherapy in Locally Advanced Breast Cancer: A Phase I/II Trial. J Clin Oncol 2003; 21:864.

47. Perloff, M, Lesnick, GJ, Korzun, A, et al. Combination chemotherapy with mastectomy or radiotherapy for stage III breast carcinoma: a Cancer and Leukemia Group B study. J Clin Oncol 1988; 6:261.

48. Abdel-Wahab, M, Wolfson, A, Raub, W, et al. The importance of postoperative radiation therapy in multimodality management of locally advanced breast cancer: a phase II trial of neoadjuvant MVAC, surgery, and radiation. Int J Radiat Oncol Biol Phys 1998; 40:875.

49. Singletary, SE, McNeese, MD, Hortobagyi, GN. Feasibility of breast-conservation surgery after induction chemotherapy for locally advanced breast carcinoma. Cancer 1992; 69:2849.

50. Chen, AM, Meric-Bernstam, F, Hunt, KK, et al. Breast conservation after neoadjuvant chemotherapy. Cancer 2005; 103:689.

51. Lyman, GH, Giuliano, AE, Somerfield, MR, et al. American Society of Clinical Oncology Guideline Recommendations for

Sentinel Lymph Node Biopsy in Early-Stage Breast Cancer. J Clin Oncol 2005; 23:7703.

52. Huang, E, McNeese, MD, Strom, EA, et al. Locoregional treatment outcomes for inoperable anthracycline-resistant breast cancer. Int J Radiat Oncol Biol Phys 2002; 53:1225.

COIMBATORE MEDICAL COLLEGE HOSPITAL

A STUDY ON CLINICOPATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CARCINOMA

PROFORMA

Name : Age: Sex: IP.no:

Address:

Occupation:

Socioeconomic status.

CLINICAL HISTORY

1.Presenting symptoms
- 1.Swelling
- 2.Pain.
- 3.Nipple discharge
- 4.Nipple retraction
- 5.Loss of appetite and weight.
- 6.Inflammatory symptoms
  - Systemic: i}Pyrexia
    - ii}Sweating
    - iii}Malaise
  - Local: i} Pain
    - ii}Change in colour
    - iii}Edema
    - iv}Cellulitis.
- 7.Symptoms suggestive of metastasis.
  - i}Back pain
  - ii}Head ache and convulsion
  - iii}Chest symptoms
  - iv}Jaundice

v}Opposite breast Swelling

2.Past history:
H/o associated medical conditions like HT/DM/IHD/TB
H/o similar swelling in the breast.
H/o surgery for benign breast disease
3. Family history:
H/o breast cancer in 1st degree relative
4. Drug history
H/o OCP intake/HRT.
H/o previous exposure to radiation
5. Menstrual history
Age at menarche
Age at menopause
Alterations in cycles.
6. Marital history
Age at marriage:
7.Obstetric history
Parity:
Age of the patient at 1st child birth:
Age of patient at last child birth:
History and duration of breast feeding:
8.Personal history
H/o smoking and alcohol:.
Dietetic history:

EXAMINATION

PRE INDUCTION CHEMOTHERAPY STATUS

General examination:
Built/pallor/icterus/pedaledema/lymphadenopathy
Local examination.
Breast: A. Side and Quadrant involved
B. Tumour size
C. Axillary nodal status
E. Opposite breast/opposite axilla
Other systems
Abdomen:
Cardiovascular system:
Respiratory system:

Central nervous system:
Spine and Cranium:

INVESTIGATIONS:

1.FNAC Biopsy.
2.Hematological parameter
3. X-ray Chest
4. USG Abdomen and pelvis
5..ECG.

STAGING:.

NEOADJUVANT CHEMOTHERAPY:

Type of regimen:
Patient details on each cycle -Tumor status
-Axillary lymphnodal status.
-Any symptoms and signs of metastasis.
No. of cycles

TREATMENT

Type of surgery

POST INDUCTION CHEMOTHERAPY STATUS

HISTOPATHOLOGY

Primary Tumor
-Macroscopic features
-Histological features
Axillary nodal status.

POST OPERATIVE ADJUVANT CHEMOTHERAPY

Duration after surgery
Type of regimen:
No. of cycles:

FOLLOW UP:

Complaints:
Nodule/Swelling

i}Single/multiple
ii}Chest wall
iii}Axilla
iv}Supraclavicular region

Ulcerations
Arm edema
Symptoms suggestive of metastasis

General examination

Local Examination

Swelling/ulcer
Operative Scar
Tumour bed
Axilla
Supraclavicular region
Arm edema

Distant metastatic sites

Bone
Lungs and pleura
Brain
Liver
Peritoneal & Krukenburg tumor
Opposite breast and Axilla

INVESTIGATIONS:

Basic investigations

Hematological parameter

Specific investigations

1.FNAC/ Biopsy if any recurrence
2. serum Calcium /serum alkaline phosphatase
3.. Liver function test
4. X-ray Chest/spine
5..USG Abdomen and pelvis
6.CT Scan if needed.

DISEASE FREE INTERVAL.

MASTER CHART

Sl. No.	Name	Age / Sex	IP No.	Menst.	Side & quadrant	TS	AN	Stage	CH	TS	AN	Surgery	RE	DFS
1	Valliammal	58 / F	6450	Post	RUO	7	4	T3N2M0	AC	0	2	MRM & AC	-	14.5
2	Ponnammal	52 / f	1320	Post	RUO	9	4	T3N1M0	AC	3	2	MRM & AC	-	19.5
3	Thenmozhi	38 / F	12134	Post	RC	7	6	T3N1M0	AC	3	4	MRM & AC	-	21
4	Mariammal	55 / F	16120	Post	RUI	7	3	T3N1M0	AC	3	0	MRM & AC	-	20
5	Maniammal	52 / F	13240	Post	RC	10	6	T3N1M0	AC	3	4	MRM & AC	-	21
6	Santhadevi	45 / F	15310	Pre	RLO	9	3	T3N1M0	AC	2	3	MRM & AC	-	25
7	Subbammal	54 / F	11234	Post	LUO	10	5	T3N2M0	AC	7	4	MRM & AC	+	28
8	Nagammel	60 / F	1231	Post	LUO	8	5	T3N1M0	AC	2	2	MRM & AC	-	29

Sl. No.	Name	Age / Sex	IP No.	Menst.	Side & quadrant	TS	AN	Stage	CH	TS	AN	Surgery	RE	DFS
			0											
9	Suseela	58 / F	12110	Post	RLO	6	4	T4N1M0	AC	1	1	MRM & AC	+	31.5
10	Mary	43 / F	13141	Pre	LLI	8	4	T3N1M0	AC	3	0	MRM & AC	-	20
11	Saradha	45 / F	9678	Post	RUI	11	4	T3N1M0	AC	6	4	MRM & AC	-	21
12	Vellammal	65 / F	9780	Post	LLO	7	4	T4N1M0	AC	3	0	MRM & AC	-	20.5
13	Laxmi	46 / F	7678	Pre	RUO	8	4	T3N1M0	AC	2	0	MRM & AC	-	17
14	Manonmani	52 / F	11658	Post	RUO	9	3	T3N1M0	AC	4	1	MRM & AC	-	12
15	Jeyalakshmi	50 / F	10076	Pre	RUO	6	3	T3N1M0	AC	0	0	MRM & AC	-	32.5
16	Parvathi	50 / F	10245	Pre	LC	5	4	T4N1M0	AC	1	1	MRM & AC	+	33.5
17	Vijaya	48 / F	1711	Post	LUI	10	5	T4N1M0	AC	9	4	MRM & AC	+	33

Sl. No.	Name	Age / Sex	IP No.	Menst.	Side & quadrant	TS	AN	Stage	CH	TS	AN	Surgery	RE	DFS
			8											
18	Meenakchi	46 / F	12787	Pre	LLO	8	6	T4N1M0	AC	6	4	MRM & AC	-	32
19	Subbathal	60 / F	7447	Post	LUI	8	4	T4NIM0	AC	8	5	MRM & AC	+	32
20	Akkammal	61 / F	22331	Post	LC	9	5	T4N1M0	AC	7	5	MRM & AC	+	30
21	Saraswathi	56 / F	7176	Post	LUO	5	5	T4N1M0	AC	2	2	MRM & AC	+	32
22	Radha	45 / F	11475	Pre	LUO	7	4	T3N1M0	AC	2	1	MRM & AC	+	30
23	Kannammal	60 / F	17118	Post	LUO	9	5	T4N2M0	AC	2	4	MRM & AC	-	28.5
24	Sivagami	56 / F	12778	Post	RLO	10	6	T3N1M0	AC	6	4	MRM & AC	-	26.5
25	Pappathi	40 / F	12147	Pre	RLI	8	0	T3N0M0	AC	2	0	MRM & AC	-	21

Sl. No.	Name	Age / Sex	IP No.	Menst.	Side & quadrant	TS	AN	Stage	CH	TS	AN	Surgery	RE	DFS
26	Shanthi	48 / F	6467	Post	RUI	9	3	T3N1M0	AC	5	1	MRM & AC	-	19
27	Petchiammal	51 / F	5467	Post	RUI	6	0	T4N0M0	AC	2	0	MRM & AC	-	13
28	Dhanalakshmi	50 / F	15117	Pre	RUO	7	3	T3N1M0	AC	4	1	MRM & AC	-	20
29	Pappaye	62 / F	14778	Post	RUO	8	4	T4N2M0	AC	0	0	MRM & AC	+	34
30	Ponnammal	55 / F	12546	Post	RUO	8	5	T3N1M0	AC	0	0	MRM & AC	-	18

Menst	-	Menopausal Status	LLI	-	Left Lower Inner
TS	-	Tumour size	MRM & AC	-	Modified Radical Mastectomy and Axillary Clearance
AN	-	Axillary Node	RC	-	Right central.
CH	-	Chemotherapy Regimen	LC	-	Left central.
RE	-	Recurrence			
DFS	-	Disease Free Survival in months			
RUO	-	Right Upper Outer			
RUI	-	Right Upper Inner			
LUO	-	Lower Upper Outer			
LUI	-	Right Upper Outer			
RLO	-	Right Lower Outer			
RLI	-	Right Lower Inner			
LLO	-	Left Lower Outer			